Height as a Sex-Cancer Mediator? Interpret With Caution

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In this issue of the Journal, Walter and colleagues (1) note three phenomena—1) men are at higher risk than women for developing many shared anatomic site cancers; 2) on average, men are taller than women; and 3) taller height is associated with higher risk for some cancers in both sexes—and question whether men might be at higher risk for some cancers because they are taller. The authors investigate the hypothesis that height mediates the relationships between sex and some cancers by applying a series of mediation analyses to data from the Vitamins and Lifestyle (VITAL) Study (2). The authors evaluate 10 specific anatomical sites and four combined sites via Cox proportional hazard models using time to cancer diagnosis as the outcome (with and without a large number of potential control variables). This editorial will focus on statistical and methodological issues in Walker et al’s assessments of mediation relations. Although we will point out some limitations, we applaud the application of mediation analysis to better understand the mechanisms by which sex and some cancers may be related. We hope that future research will 1) continue to investigate the role height may play in mediating relationships between sex or other explanatory variables and cancers and 2) use mediation analysis to better understand mechanisms that relate to other associated variables in cancer research.

The authors transform the height variable, using a quadratic parameterization (height and height squared), to reflect the mechanism by which height is hypothesized to transmit the effect from sex to cancer: an increased number of cells at risk “proportional to a two-dimensional surface area” (1). However, we question whether this quadratic version of height effectively captures the hypothesized two-dimensional surface area rather than simply assessing whether the relationship between height and cancer differs at varying levels of height (ie, a curvilinear relationship). Ideally, the authors would also assess a simpler model of unparameterized height, which, if found to be an adequate explanatory variable, could stimulate thinking about alternative height-related mechanisms.

Tests for mediation assess whether some third variable, M, mediates the relationship between X and Y, such that X has a causal effect on M, which in turn has a causal effect on Y. A mediating variable is statistically equivalent to the conceptually distinct confounder variable (3). The distinctive conceptual difference is that a mediator is part of a causal sequence of events. Consequently, researchers should have theoretical support for the mediation model and include potentially important confounders to maximize the ability to make causal inferences (4). Given that sex or height can never be randomly assigned, conclusions about causation must be made with extreme caution. In fact, many methodologists have argued that causal inference cannot be inferred for variables that could not possibly be observed under counterfactual conditions (eg, sex) (5,6). Regardless, we feel that with careful methodology, valuable information can be obtained regarding the potential for causal inference with sex. To help address this issue, the authors include a large set of covariates known to be associated with cancer to minimize the threat of missing confounders, but there may be other variables affecting the relationship between both sex and cancers (eg, the authors rightfully acknowledge the absence of occupational exposures as a potential confounder). Even though the inclusion of the full set of measured potential confounders was the more justifiable approach, the manuscript highlights results from the analyses without these covariates. For analyses that included all measured potential confounders, only melanoma provides evidence of a mediational relationship. An important potential confounder for melanoma, sun exposure, is included, but the measure is only assessed with a single “yes/no” question regarding the experience of three or more serious sunburns. It is possible that a more nuanced measure of sun exposure could account for sex differences in melanoma. And although the known important confounders were generally included, it is possible that there are still confounders missing. Further exploration of the data could consider sensitivity analyses (7) to assess the potential importance of omitted confounders or use propensity score methods (8,9) to help address omitted variable

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References
5. Test for mediation assess whether some third variable, M, mediates the relationship between X and Y, such that X has a causal effect on M, which in turn has a causal effect on Y. A mediating variable is statistically equivalent to the conceptually distinct con- confounder variable (3). The distinctive conceptual difference is that a mediator is part of a causal sequence of events. Consequently, researchers should have theoretical support for the mediation model and include potentially important confounders to maximize the ability to make causal inferences (4). Given that sex or height can never be randomly assigned, conclusions about causation must be made with extreme caution. In fact, many methodologists have argued that causal inference cannot be inferred for variables that could not possibly be observed under counterfactual conditions (eg, sex) (5,6). Regardless, we feel that with careful methodology, valuable information can be obtained regarding the potential for causal inference with sex. To help address this issue, the authors include a large set of covariates known to be associated with cancer to minimize the threat of missing confounders, but there may be other variables affecting the relationship between both sex and cancers (eg, the authors rightfully acknowledge the absence of occupational exposures as a potential confounder). Even though the inclusion of the full set of measured potential confounders was the more justifiable approach, the manuscript highlights results from the analyses without these covariates. For analyses that included all measured potential confounders, only melanoma provides evidence of a mediational relationship. An important potential confounder for melanoma, sun exposure, is included, but the measure is only assessed with a single “yes/no” question regarding the experience of three or more serious sunburns. It is possible that a more nuanced measure of sun exposure could account for sex differences in melanoma. And although the known important confounders were generally included, it is possible that there are still confounders missing. Further exploration of the data could consider sensitivity analyses (7) to assess the potential importance of omitted confounders or use propensity score methods (8,9) to help address omitted variable

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explanations. The extent to which the authors believe they have met the other assumptions of mediation is unclear. The temporal precedence assumption requires that the “assignment” of sex precedes attainment of height, and that the attainment of height precedes the development of cancer. Although it can be argued that sex precedes height in time, it can also be argued that assignment of sex occurs simultaneously with an assignment of height at conception (assuming environmental implications on height are minimal). This theoretical interpretation of the variables in question in part determines whether this study represents noncausal associations or a mediational relationship.

Another important consideration is the method used to assess and quantify mediational effects. The authors compare the coefficient predicting the log hazard of cancer by sex in the model without height and height squared (used as an estimate of the total effect of sex on cancer risk) to the corresponding coefficient in the model including height and height squared (used as an estimate of the direct effect of sex on cancer risk), thus employing the “difference method” of estimating the indirect effect (10); they use the ratio of these indirect effect and total effect estimates to estimate the proportion mediated. The authors note that the validity of these methods of estimation is based on the rough equivalence of the “product method” (10) and the difference method of estimating indirect effects in proportional hazards models with rare events (11); when there is potential for inequivalence between the difference and product methods, interpretation of the mediated effect should be approached with caution. Furthermore, Pearl (12) has shown that for nonlinear models, estimating mediated effects is not so straightforward. The inclusion of a nonlinear height term adds increasing difficulty to the quantification and interpretation of mediated effects. Mediation with survival data and nonlinear terms is an active area of investigation, and additional guidance in the literature should be forthcoming.

Although we have pointed out potential limitations with the analyses, we applaud the authors for applying mediation analyses to better understand the mechanisms by which sex is associated with cancer. To the extent that height as mediator has not previously been considered, the authors make a valuable contribution to the literature. The article demonstrates that the occurrence of many types of shared site cancers is associated with both sex and height. We caution against interpreting the results from the models without the full set of covariates as causal mediation effects. Melanoma shows the strongest support for a mediational relationship, albeit with assumptions that may or may not be met. Future studies should address additional confounding factors and violations of mediation assumptions to help clarify the results. Ultimately, a careful plan of follow-up studies may lead to a better understanding of the role that height, or factors related to height, might play in cancer development.

References

Note
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Trichloroethylene and Cancer

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Trichloroethylene (TCE) was for many decades the solvent of choice for cleaning and vapor degreasing of metal parts, and has been commonly used in several other industrial applications. Since the early 1970s, however, concern over potential risks of cancer and other health effects among TCE-exposed workers, coupled with its documented environmental release through air and wastewater emissions, has led to a decline in its use. Strong evidence of carcinogenicity has come from experimental